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Active Ingredient Search Results from "Rx" table for query on "bleomycin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
065042	AP	No	BLEOMYCIN SULFATE	Injectable; Injection	EQ 15 UNITS BASE/VIAL	BLEOMYCIN	BEDFORD
065042	AP	No	BLEOMYCIN SULFATE	Injectable; Injection	EQ 30 UNITS BASE/VIAL	BLEOMYCIN	BEDFORD
050443	AP	Yes	BLEOMYCIN SULFATE	Injectable; Injection	EQ 15 UNITS BASE/VIAL	BLENOXANE	BRISTOL MYERS SQUIBB
050443	AP	Yes	BLEOMYCIN SULFATE	Injectable; Injection	EQ 30 UNITS BASE/VIAL	BLENOXANE	BRISTOL MYERS SQUIBB
065031	AP	No	BLEOMYCIN SULFATE	Injectable; Injection	EQ 15 UNITS BASE/VIAL	BLEOMYCIN	FAULDING
065031	AP	No	BLEOMYCIN SULFATE	Injectable; Injection	EQ 30 UNITS BASE/VIAL	BLEOMYCIN	FAULDING
065033	AP	No	BLEOMYCIN SULFATE	Injectable; Injection	EQ 15 UNITS BASE/VIAL	BLEOMYCIN	GENSIA SICOR PHARMS
064084	AP	No	BLEOMYCIN SULFATE	Injectable; Injection	EQ 15 UNITS BASE/VIAL	BLEOMYCIN SULFATE	GENSIA SICOR PHARMS
064084	AP	No	BLEOMYCIN SULFATE	Injectable; Injection	EQ 30 UNITS BASE/VIAL	BLEOMYCIN SULFATE	GENSIA SICOR PHARMS
065033	AP	No	BLEOMYCIN SULFATE	Injectable; Injection	EQ 30 UNITS BASE/VIAL	BLEOMYCIN	GENSIA SICOR PHARMS

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Active Ingredient Search Results from "Rx" table for query on "daunorubicin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050704		Yes	DAUNORUBICIN CITRATE	Injectable, Liposomal; Injection	EQ 2MG BASE/ML	DAUNOXOME	GILEAD
064103	AP	Yes	DAUNORUBICIN HYDROCHLORIDE	Injectable; Injection	EQ 20MG BASE/VIAL	CERUBIDINE	BEDFORD
050731	AP	Yes	DAUNORUBICIN HYDROCHLORIDE	Injectable; Injection	EQ 5MG BASE/ML	DAUNORUBICIN HCL	BEDFORD
065000	AP	No	DAUNORUBICIN HYDROCHLORIDE	Injectable; Injection	EQ 20MG BASE/VIAL	DAUNORUBICIN HCL	BIGMAR
064212	AP	No	DAUNORUBICIN HYDROCHLORIDE	Injectable; Injection	EQ 20MG BASE/VIAL	DAUNORUBICIN HCL	GENSIA SICOR PHARMS
064212		Yes	DAUNORUBICIN HYDROCHLORIDE	Injectable; Injection	EQ 50MG BASE/VIAL	DAUNORUBICIN HCL	GENSIA SICOR PHARMS
065035	AP	No	DAUNORUBICIN HYDROCHLORIDE	Injectable; Injection	EQ 5MG BASE/ML	DAUNORUBICIN HCL	GENSIA SICOR PHARMS
065034	AP	No	DAUNORUBICIN HYDROCHLORIDE	Injectable; Injection	EQ 5MG BASE/VIAL	DAUNORUBICIN HCL	SUPERGEN

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Active Ingredient Search Results from "Rx" table for query on "doxorubicin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050718		Yes	DOXORUBICIN HYDROCHLORIDE	Injectable, Liposomal; Injection	2MG/ML	DOXIL	ALZA
063277	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	2MG/ML	DOXORUBICIN HCL	AM PHARM PARTNERS
062921	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	10MG/VIAL	DOXORUBICIN HCL	BEDFORD
064097	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	200MG/100ML	DOXORUBICIN HCL	BEDFORD
062921	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	20MG/VIAL	DOXORUBICIN HCL	BEDFORD
062975	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	2MG/ML	DOXORUBICIN HCL	BEDFORD
062921	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	50MG/VIAL	DOXORUBICIN HCL	BEDFORD
062926		No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	100MG/VIAL	RUBEX	BRISTOL MYERS SQUIBB
062926	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	10MG/VIAL	RUBEX	BRISTOL MYERS SQUIBB
062926	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	50MG/VIAL	RUBEX	BRISTOL MYERS SQUIBB
064140	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	200MG/100ML	DOXORUBICIN HCL	GENSIA SICOR PHARMS
064140	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	2MG/ML	DOXORUBICIN HCL	GENSIA SICOR PHARMS
063097	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	10MG/VIAL	DOXORUBICIN HCL	PHARMACHEMIE
063336	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	200MG/100ML	DOXORUBICIN HCL	PHARMACHEMIE
063097	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	20MG/VIAL	DOXORUBICIN HCL	PHARMACHEMIE
063336	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	2MG/ML	DOXORUBICIN HCL	PHARMACHEMIE
063097	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	50MG/VIAL	DOXORUBICIN HCL	PHARMACHEMIE
050467	AP	Yes	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	10MG/VIAL	ADRIAMYCIN RDF	PHARMACIA AND UPJOHN
050629	AP	Yes	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	200MG/100ML	ADRIAMYCIN PFS	PHARMACIA AND UPJOHN
063165	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	200MG/100ML	ADRIAMYCIN PFS	PHARMACIA AND UPJOHN
050467	AP	Yes	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	20MG/VIAL	ADRIAMYCIN RDF	PHARMACIA AND UPJOHN
063165	AP	No	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	2MG/ML	ADRIAMYCIN PFS	PHARMACIA AND UPJOHN
050629	AP	Yes	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	2MG/ML	ADRIAMYCIN PFS	PHARMACIA AND UPJOHN
050467	AP	Yes	DOXORUBICIN HYDROCHLORIDE	Injectable; Injection	50MG/VIAL	ADRIAMYCIN RDF	PHARMACIA AND UPJOHN

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Active Ingredient Search Results from "Rx" table for query on "epirub."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050778	BX	Yes	EPIRUBICIN HYDROCHLORIDE	Injectable; Injection	2MG/ML	ELLENCE	PHARMACIA AND UPJOHN

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Active Ingredient Search Results from "Rx" table for query on "mitomycin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
064180	AP	No	MITOMYCIN	Injectable; Injection	20MG/VIAL	MITOMYCIN	BAXTER HLTHCARE
064180	AP	No	MITOMYCIN	Injectable; Injection	5MG/VIAL	MITOMYCIN	BAXTER HLTHCARE
064117	AP	No	MITOMYCIN	Injectable; Injection	20MG/VIAL	MITOMYCIN	BEDFORD
064117	AP	No	MITOMYCIN	Injectable; Injection	5MG/VIAL	MITOMYCIN	BEDFORD
062336	AP	Yes	MITOMYCIN	Injectable; Injection	20MG/VIAL	MUTAMYCIN	BRISTOL MYERS
062336		Yes	MITOMYCIN	Injectable; Injection	40MG/VIAL	MUTAMYCIN	BRISTOL MYERS
062336	AP	Yes	MITOMYCIN	Injectable; Injection	5MG/VIAL	MUTAMYCIN	BRISTOL MYERS
064106	AP	No	MITOMYCIN	Injectable; Injection	20MG/VIAL	MITOMYCIN	FAULDING
064144	AP	No	MITOMYCIN	Injectable; Injection	20MG/VIAL	MITOMYCIN	SUPERGEN
064144	AP	No	MITOMYCIN	Injectable; Injection	5MG/VIAL	MITOMYCIN	SUPERGEN
050763		Yes	MITOMYCIN	Injectable; Injection	5MG/VIAL	MYTOZYTREX	SUPERGEN

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Active Ingredient Search Results from "Rx" table for query on "plicamycin."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
050109		Yes	PLICAMYCIN	Injectable; Injection	2.5MG/VIAL	MITHRACIN	PFIZER

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Rx only

BLENOXANE®

(bleomycin sulfate for injection, USP):

Formerly known as: **sterile bleomycin sulfate, USP**

WARNING

It is recommended that BLENOXANE be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Pulmonary fibrosis is the most severe toxicity associated with BLENOXANE. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis. Its occurrence is higher in elderly patients and in those receiving greater than 400 units total dose, but pulmonary toxicity has been observed in young patients and those treated with low doses.

A severe idiosyncratic reaction consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with BLENOXANE.

DESCRIPTION

BLENOXANE® (bleomycin sulfate for injection, USP) is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*. It is freely soluble in water.

Note: A unit of bleomycin is equal to the formerly used milligram activity. The term milligram activity is a misnomer and was changed to units to be more precise.

CLINICAL PHARMACOLOGY

Although the exact mechanism of action of BLENOXANE is unknown, available evidence would seem to indicate that the main mode of action is the inhibition of DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

In mice, high concentrations of BLENOXANE are found in the skin, lungs, kidneys, peritoneum, and lymphatics. Tumor cells of the skin and lungs have been found to have high concentrations of BLENOXANE in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of BLENOXANE found in bone marrow may be related to high levels of BLENOXANE degradative enzymes found in that tissue.

In patients with normal renal function, 60% to 70% of an administered dose is recovered in the urine as active bleomycin. In patients with a creatinine clearance of >35 mL per minute, the serum or plasma terminal elimination half-life of bleomycin is approximately 115 minutes. In patients with a creatinine clearance of <35 mL per minute, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. It was reported that patients with moderately severe renal failure excreted less than 20% of the dose in the urine. This result would suggest that severe renal impairment could lead to accumulation of the drug in blood.

Information on the dose proportionality of bleomycin is not available.

When administered intrapleurally for the treatment of malignant pleural effusion, BLENOXANE acts as a sclerosing agent.

Following intrapleural administration to a limited number of patients (n=4), the resultant bleomycin plasma concentrations suggest a systemic absorption of approximately 45%.

The safety and efficacy of BLENOXANE 60 units and tetracycline (1 gm) as treatment for malignant pleural effusion were evaluated in a multicenter, randomized trial. Patients were required to have cytologically positive pleural effusion, good performance status (0,1,2), lung re-expansion following tube thoracostomy with drainage rates of 100 mL/24 hr. or less, no prior intrapleural therapy, no prior systemic BLENOXANE therapy, no chest irradiation and no recent change in systemic therapy Overall survival did not differ between the BLENOXANE 60 units (n=44) and tetracycline (n=41) groups. Of patients evaluated within 30 days of instillation, the

recurrence rate was 36% (10/28) with BLENOXANE and 67% (18/27) with tetracycline (p=0.023). Toxicity was similar between groups.

INDICATIONS AND USAGE

BLENOXANE should be considered a palliative treatment. It has been shown to be useful in the management of the following neoplasms either as a single agent or in proven combinations with other approved chemotherapeutic agents:

Squamous Cell Carcinoma

Head and neck (including mouth, tongue, tonsil, nasopharynx, oropharynx, sinus, palate, lip, buccal mucosa, gingivae, epiglottis, skin, larynx), penis, cervix, and vulva. The response to BLENOXANE is poorer in patients with previously irradiated head and neck cancer.

Lymphomas

Hodgkin's disease, non-Hodgkin's lymphoma.

Testicular Carcinoma

Embryonal cell, choriocarcinoma, and teratocarcinoma.

BLENOXANE has also been shown to be useful in the management of:

Malignant Pleural Effusion

BLENOXANE is effective as a sclerosing agent for the treatment of malignant pleural effusion and prevention of recurrent pleural effusions.

CONTRAINDICATIONS

BLENOXANE is contraindicated in patients who have demonstrated a hypersensitive or an idiosyncratic reaction to it.

WARNINGS

Patients receiving BLENOXANE must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function.

Pulmonary toxicities occur in 10% of treated patients. In approximately 1%, the nonspecific pneumonitis induced by BLENOXANE progresses to pulmonary fibrosis, and death. Although this is age and dose related, the toxicity is unpredictable. Frequent roentgenograms are recommended (see **ADVERSE REACTIONS: Pulmonary** section).

A severe idiosyncratic reaction (similar to anaphylaxis) consisting of hypotension, mental confusion, fever, chills, and wheezing has been reported in approximately 1% of lymphoma patients treated with BLENOXANE. Since these reactions usually occur after the first or second dose, careful monitoring is essential after these doses (see **ADVERSE REACTIONS: Idiosyncratic Reactions** section).

Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported, infrequently. These toxicities may occur, however, at any time after initiation of therapy.

Usage in Pregnancy

Pregnancy Category D

BLENOXANE can cause fetal harm when administered to a pregnant woman. It has been shown to be teratogenic in rats. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a unit/m^2 basis) on days 6–15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. BLENOXANE is abortifacient but not teratogenic in rabbits, at i.v. doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a unit/m^2 basis) given on gestation days 6–18.

There have been no studies in pregnant women. If BLENOXANE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with BLENOXANE.

PRECAUTIONS

General

Bleomycin clearance may be reduced in patients with impaired renal function. No guidelines have been established for dose adjustments, but bleomycin should be used with extreme caution in patients with significant renal impairment.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

The carcinogenic potential of BLENOXANE in humans is unknown. A study in F344-type male rats demonstrated an increased incidence of nodular hyperplasia after induced lung carcinogenesis by nitrosamines, followed by treatment with bleomycin. In another study where the drug was administered to rats by subcutaneous injection at 0.35 mg/kg weekly (3.82 units/m^2 weekly or about 30% at the recommended human dose), necropsy findings included dose related injection site fibrosarcomas as well as various renal tumors. Bleomycin has been shown to be mutagenic both *in vitro* and *in vivo*. The effects of bleomycin on fertility have not been studied

Pregnancy

Pregnancy Category D (see **WARNINGS** section).

Nursing Mothers

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued by women receiving BLENOXANE therapy.

Pediatric Use

Safety and effectiveness of BLENOXANE in pediatric patients have not been established.

Geriatric Use

In clinical trials, pulmonary toxicity was more common in patients older than 70 years than in younger patients (see **BOX WARNING**, **WARNINGS**, and **ADVERSE REACTIONS: Pulmonary**). Other reported clinical experience has not identified other differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Bleomycin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Pulmonary

This is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent presentation is pneumonitis occasionally progressing to pulmonary fibrosis Approximately 1% of patients treated have died of pulmonary fibrosis. Pulmonary toxicity is both dose and age related, being more common in patients over 70 years of age and in those receiving over 400 units total dose. This toxicity, however, is unpredictable and has been seen occasionally in young patients receiving low doses. Some published reports have suggested that the risk of pulmonary toxicity may be increased when bleomycin is used in combination with G-CSF (filgrastim) or other cytokines. However, randomized clinical studies completed to date have not demonstrated an increased risk of pulmonary complications in patients treated with bleomycin and G-CSF.

Because of lack of specificity of the clinical syndrome, the identification of patients with pulmonary toxicity due to BLENOXANE (bleomycin sulfate for injection, USP) has been extremely difficult. The earliest symptom associated with BLENOXANE pulmonary toxicity is dyspnea. The earliest sign is fine rales.

Radiographically, BLENOXANE-induced pneumonitis produces nonspecific patchy opacities, usually of the lower lung fields. The most common changes in pulmonary function tests are a decrease in total lung volume and a decrease in vital

capacity. However, these changes are not predictive of the development of pulmonary fibrosis.

The microscopic tissue changes due to BLENOXANE toxicity include bronchiolar squamous metaplasia, reactive macrophages, atypical alveolar epithelial cells, fibrinous edema, and interstitial fibrosis. The acute stage may involve capillary changes and subsequent fibrinous exudation into alveoli producing a change similar to hyaline membrane formation and progressing to a diffuse interstitial fibrosis resembling the Hamman-Rich syndrome. These microscopic findings are nonspecific; eg, similar changes are seen in radiation pneumonitis and pneumocystic pneumonitis.

To monitor the onset of pulmonary toxicity, roentgenograms of the chest should be taken every 1 to 2 weeks (see **WARNINGS** section). If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Recent studies have suggested that sequential measurement of the pulmonary diffusion capacity for carbon monoxide (DL_{CO}) during treatment with BLENOXANE may be an indicator of subclinical pulmonary toxicity. It is recommended that the DL_{CO} be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DL_{CO} falls below 30% to 35% of the pretreatment value.

Because of bleomycin's sensitization of lung tissue, patients who have received bleomycin are at greater risk of developing pulmonary toxicity when oxygen is administered in surgery. While long exposure to very high oxygen concentrations is a known cause of lung damage, after bleomycin administration, lung damage can occur at lower concentrations that are usually considered safe. Suggested preventive measures are:

1. Maintain FIO_2 at concentrations approximating that of room air (25%) during surgery and the postoperative period.

2. Monitor carefully fluid replacement, focusing more on colloid administration rather than crystalloid.

Sudden onset of an acute chest pain syndrome suggestive of pleuropericarditis has been rarely reported during BLENOXANE infusions. Although each patient must be individually evaluated, further courses of BLENOXANE do not appear to be contraindicated.

Pulmonary adverse events which may be related to the intrapleural administration of BLENOXANE have been reported only rarely.

Idiosyncratic Reactions

In approximately 1% of the lymphoma patients treated with BLENOXANE (bleomycin sulfate for injection, USP), an idiosyncratic reaction, similar to anaphylaxis clinically, has been reported. The reaction may be immediate or delayed for several hours, and usually occurs after the first or second dose (see **WARNINGS** section). It consists of hypotension, mental confusion, fever, chills, and wheezing. Treatment is symptomatic including volume expansion, pressor agents, antihistamines, and corticosteroids.

Integument and Mucous Membranes

These are the most frequent side effects, being reported in approximately 50% of treated patients. These consist of erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of the skin. Hyperkeratosis, nail changes, alopecia, pruritus, and stomatitis have also been reported. It was necessary to discontinue BLENOXANE therapy in 2% of treated patients because of these toxicities.

Scleroderma-like skin changes have also been reported as part of postmarketing surveillance.

Skin toxicity is a relatively late manifestation usually developing in the 2nd and 3rd week of treatment after 150 to 200 units of BLENOXANE have been administered and appears to be related to the cumulative dose.

Intrapleural administration of BLENOXANE has occasionally been associated with local pain. Hypotension possibly requiring symptomatic treatment has been reported infrequently. Death has been very rarely reported in association with BLENOXANE pleurodesis in these very seriously ill patients.

Other

Vascular toxicities coincident with the use of BLENOXANE in combination with other antineoplastic agents have been reported rarely. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (HUS) or cerebral arteritis. Various mechanisms have been proposed

for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with BLENOXANE in combination with vinblastine with or without cisplatin or, in a few cases, with BLENOXANE as a single agent. It is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, BLENOXANE, vinblastine, hypomagnesemia, or a combination of any of these factors.

Fever, chills, and vomiting were frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions were reported infrequently.

Malaise was also reported as part of postmarketing surveillance.

DOSAGE AND ADMINISTRATION

Because of the possibility of an anaphylactoid reaction, lymphoma patients should be treated with 2 units or less for the first two doses. If no acute reaction occurs, then the regular dosage schedule may be followed.

The following dose schedule is recommended: **Squamous cell carcinoma, non-Hodgkin's lymphoma, testicular carcinoma**—0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly.

Hodgkin's Disease—0.25 to 0.50 units/kg (10 to 20 units/m^2) given intravenously, intramuscularly, or subcutaneously weekly or twice weekly. After a 50% response, a maintenance dose of 1 unit daily or 5 units weekly intravenously or intramuscularly should be given.

Pulmonary toxicity of BLENOXANE appears to be dose related with a striking increase when the total dose is over 400 units. Total doses over 400 units should be given with great caution.

Note: When BLENOXANE (bleomycin sulfate for injection, USP), is used in combination with other antineoplastic agents, pulmonary toxicities may occur at lower doses.

Improvement of Hodgkin's disease and testicular tumors is prompt and noted within 2 weeks. If no improvement is seen by this time, improvement is unlikely.

Squamous cell cancers respond more slowly, sometimes requiring as long as 3 weeks before any improvement is noted.

Malignant Pleural Effusion—60 units administered as a single dose bolus intrapleural injection (see **ADMINISTRATION: Intrapleural** section).

Administration

BLENOXANE may be given by the intramuscular, intravenous, subcutaneous or intrapleural routes.

Intramuscular or Subcutaneous

The BLENOXANE 15 units vial should be reconstituted with 1 to 5 mL of Sterile Water for Injection, USP, Sodium Chloride for Injection, 0.9%, USP, or Sterile Bacteriostatic Water for Injection, USP. The BLENOXANE 30 units vial should be reconstituted with 2 to 10 mL of the above diluents.

Intravenous

The contents of the 15 units or 30 units vial should be dissolved in 5 mL or 10 mL, respectively of Sodium Chloride for Injection, 0.9%, USP and administered slowly over a period of 10 minutes.

Intrapleural

60 units of BLENOXANE is dissolved in 50–100 mL sodium chloride injection 0.9%, and administered through a thoracostomy tube following drainage of excess pleural fluid and confirmation of complete lung expansion. The literature suggests that successful pleurodesis is, in part, dependent upon complete drainage of the pleural fluid and reestablishment of negative intrapleural pressure prior to instillation of a sclerosing agent. Therefore, the amount of drainage from the chest tube should be as minimal as possible prior to instillation of BLENOXANE. Although there is no conclusive evidence to support this contention, it is generally accepted that chest tube drainage should be less than 100 mL in a 24 hour period prior to sclerosis. However, BLENOXANE instillation may be appropriate when drainage is between 100–300 mL under clinical conditions that necessitate sclerosis therapy. The thoracostomy tube is clamped after BLENOXANE instillation. The patient is moved from the supine to the left and right lateral positions

several times during the next four hours. The clamp is then removed and suction reestablished. The amount of time the chest tube remains in place following sclerosis is dictated by the clinical situation.

The intrapleural injection of topical anesthetics or systemic narcotic analgesia is generally not required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

BLENOXANE® (bleomycin sulfate for injection, USP) is available as follows:

NDC 0015-3010-20, 15 units per vial as bleomycin sulfate for injection, USP.

NDC 0015-3063-01, 30 units per vial as bleomycin sulfate for injection, USP.

Stability

The sterile powder is stable under refrigeration 2° C (36° F) to 8° C (46° F) and should not be used after the expiration date is reached.

BLENOXANE should not be reconstituted or diluted with D_5W or other dextrose containing diluents. When reconstituted in D_5W and analyzed by HPLC, BLENOXANE demonstrates a loss of A_2 and B_2 potency that does not occur when BLENOXANE is reconstituted in 0.9% Sodium Chloride.

BLENOXANE is stable for 24 hours at room temperature in Sodium Chloride.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.

2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, 1985; 253(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure--Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD, Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia* 1983; 1:426-428.

5. Jones RB, et al: Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *CA–A Cancer Journal for Clinicians* 1983; (Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990 ;47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA WORK PRACTICE GUIDELINES). *Am J Health-Syst Pharm* 1996; 53:1669-1685.

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Doxorubicin Hydrochloride for Injection, USP

Doxorubicin Hydrochloride Injection, USP

Rx Only

FOR INTRAVENOUS USE ONLY

WARNING

1. Severe local tissue necrosis will occur if there is extravasation during administration (see DOSAGE AND ADMINISTRATION). Doxorubicin must not be given by the intramuscular or subcutaneous route.

2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The probability of developing impaired myocardial function based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m^2 of doxorubicin, 3 to 5% at a dose of 400 mg/m^2, 5 to 8% at 450 mg/m^2 and 6 to 20% at 500 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 400 mg/m^2. Risk factors (active or dormant cardiovascular disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, concomitant use of other cardiotoxic drugs) may increase the risk of cardiac toxicity. Cardiac toxicity with doxorubicin may occur at lower cumulative doses whether or not cardiac risk factors are present. Pediatric patients are at increased risk for developing delayed cardiotoxicity.

3. Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) has been reported in patients treated with anthracyclines, including doxorubicin (see ADVERSE REACTIONS). The occurrence of refractory secondary AML or MDS is more common when anthracyclines are given in combination with DNA-damaging anti-neoplastic agents or radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been escalated. The rate of developing secondary AML or MDS has

been estimated in an analysis of 8563 patients with early breast cancer treated in 6 studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), including NSABP B-15. Patients in these studies received standard doses of doxorubicin and standard or escalated doses of cyclophosphamide (AC) adjuvant chemotherapy and were followed for 61,810 patient years. Among 4483 such patients who received conventional doses of AC, 11 cases of AML or MDS were identified, for an incidence of 0.32 cases per 1000 patient years (95% CI 0.16-0.57) and a cumulative incidence at 5 years of 0.21% (95% CI 0.11-.41%). In another analysis of 1474 patients with breast cancer who received adjuvant treatment with doxorubicin-containing regimens in clinical trials conducted at University of Texas M.D. Anderson Cancer Center, the incidence was estimated at 1.5% at 10 years. In both experiences, patients who received regimens with higher cyclophosphamide dosages, who received radiotherapy, or who were aged 50 or older had an increased risk of secondary AML or MDS. Pediatric patients are also at risk of developing secondary AML.

4. Dosage should be reduced in patients with impaired hepatic function.
5. Severe myelosuppression may occur.
6. Doxorubicin should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents.

DESCRIPTION

Doxorubicin is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* var. *caesius*. Doxorubicin consists of a naphthacenequinone nucleus linked through a glycosidic bond at ring atom 7 to an amino sugar, daunosamine. Chemically, doxorubicin hydrochloride is: 5,12-Naphthacenedione, 10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxylacetyl)-1-methoxy-, hydrochloride (8S-*cis*)-. The structural formula is as follows:

[INSERT STRUCTURE]

Doxorubicin binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino

sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as plasma proteins.

Doxorubicin Hydrochloride for Injection, USP, is a sterile red-orange lyophilized powder.

Doxorubicin Hydrochloride Injection, USP, is a sterile parenteral, isotonic solution.

CLINICAL PHARMACOLOGY

The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity.

Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generates highly reactive species including the hydroxyl free radical $OH^{\bullet}$. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level.

Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both

Animal studies have shown activity in a spectrum of experimental tumors, immunosuppression, carcinogenic properties in rodents, induction of a variety of toxic effects, including delayed and progressive cardiac toxicity, myelosuppression in all species and atrophy to testes in rats and dogs.

Pharmacokinetics

Pharmacokinetic studies, determined in patients with various types of tumors undergoing either single or multi-agent therapy have shown that doxorubicin follows a multiphasic disposition after intravenous injection. In four patients, doxorubicin has demonstrated dose-independent pharmacokinetics in the dose range of 30 to 70 mg/m^2.

Distribution. The initial distribution half-life of approximately 5 minutes suggests rapid tissue uptake of doxorubicin, while its slow elimination from tissues is reflected by a terminal half-life of 20 to 48 hours. Steady-state distribution volume ranges from 809 to 1214 L/m^2 and is indicative of extensive drug uptake into tissues. Binding of doxorubicin and its major metabolite, doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin up to 1.1 μg/mL.

Doxorubicin was excreted in the milk of one lactating patient, with peak milk concentration at 24 hours after treatment being approximately 4.4-fold greater than the corresponding plasma concentration. Doxorubicin was detectable in the milk up to 72 hours after therapy with 70 mg/m^2 of doxorubicin given as a 15-minute intravenous infusion and 100 mg/m^2 of cisplatin as a 26-hour intravenous infusion. The peak concentration of doxorubicinol in milk at 24 hours was 0.11 μg/mL and AUC up to 24 hours was 9.0 μg.h/mL while the AUC for doxorubicin was 5.4 μg.h/mL.

Doxorubicin does not cross the blood brain barrier.

Metabolism. Enzymatic reduction at the 7 position and cleavage of the daunosamine sugar yields aglycones which are accompanied by free radical formation, the local production of which may contribute to the cardiotoxic activity of doxorubicin. Disposition of doxorubicinol (DOX-OL) in patients is formation rate limited, with the terminal half-life of DOX-OL being similar to doxorubicin. The relative exposure of DOX-OL, i.e., the ratio between the AUC of DOX-OL and the AUC of doxorubicin, compared to doxorubicin ranges between 0.4 and 0.6.

Excretion. Plasma clearance is in the range 324 to 809 mL/min/m^2 and is predominately by metabolism and biliary excretion. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. In urine, <3% of the dose was recovered as DOX-OL over 7 days.

Systemic clearance of doxorubicin is significantly reduced in obese women with ideal body weight greater than 130%. There was a significant reduction in clearance without any change in volume of distribution in obese patients when compared with normal patients with less than 115% ideal body weight.

Pharmacokinetics in Special Populations

Pediatric. Following administration of 10 to 75-mg/m^2 doses of doxorubicin to 60 children and adolescents ranging from 2 months to 20 years of age, doxorubicin clearance averaged 1443 ± 114 mL/min/m^2 . Further analysis demonstrated that clearance in 52 children greater than 2 years of age (1540 mL/min/m^2) was increased compared with adults. However, clearance in infants younger than 2 years of age (813 mL/min/m^2) was decreased compared with older children and approached the range of clearance values determined in adults.

Geriatric While the pharmacokinetics of elderly subjects (=65 years of age) have been evaluated, no dosage adjustment is recommended based on age. (See PRECAUTIONS, Geriatric Use.)

Gender. A published clinical study involving 6 men and 21 women with no prior anthracycline therapy reported a significantly higher median doxorubicin clearance in the men compared to the women (1088 mL/min/m^2 versus 433 mL/min/m^2). However, the terminal half-life of doxorubicin was longer in men compared to the women (54 versus 35 hours).

Race. The influence of race on the pharmacokinetics of doxorubicin has not been evaluated.

Hepatic Impairment. The clearance of doxorubicin and doxorubicinol was reduced in patients with impaired hepatic function (see DOSAGE & ADMINISTRATION).

Renal Impairment. The influence of renal function on the pharmacokinetics of doxorubicin has not been evaluated.

CLINICAL STUDIES

The effectiveness of doxorubicin-containing regimens in the adjuvant therapy of early breast cancer has primarily been established based on data collected in a meta-analysis published in 1998 by the Early Breast Cancer Trialists Collaborative Group (EBCTCG). The EBCTCG obtains primary data on all relevant studies, both published and unpublished, for early stage breast cancer and regularly updates these analyses. The principal endpoints for the adjuvant chemotherapy trials were disease-free survival (DFS) and overall survival (OS). The meta-analyses allowed comparisons of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to no chemotherapy (19 trials including 7523 patients) and comparisons of doxorubicin-containing regimens with CMF as an active control (6 trials including 3510 patients). The pooled estimates of DFS and OS from these trials were used to calculate the effect of CMF relative to no therapy. The hazard ratio for DFS for CMF compared to no chemotherapy was 0.76 (95% CI 0.71-0.82) and for OS was 0.86 (95% CI 0.80-0.93). Based on a conservative estimate of CMF effect (lower 2-sided 95% confidence limit of hazard ratio) and 75% retention of CMF effect on DFS, it was determined that the doxorubicin containing-regimens would be considered as non-inferior to CMF if the upper 2-sided 95% confidence limit of the hazard ratio was less than 1.06, i.e. not more than 6% worse than CMF. A similar calculation for OS would require a non-inferiority margin of 1.02.

Six randomized trials in the EBCTCG meta-analysis compared doxorubicin-containing regimens to CMF. A total of 3510 women with early breast cancer involving axillary lymph nodes were evaluated; approximately 70% were premenopausal and 30% were postmenopausal. At the time of the meta-analysis, 1745 first recurrences and 1348 deaths had occurred. Analyses demonstrated that doxorubicin-containing regimens retained at least 75% of the historical CMF adjuvant effect on DFS and are effective. The hazard ratio for DFS (dox:CMF) was 0.91 (95% CI 0.82-1.01) and for OS was 0.91 (95% CI 0.81-1.03). Results of these analyses for both DFS and OS are provided in Table 1 and Figures 1 and 2.

Table 1. Summary of Randomized Trials Comparing Doxorubicin-Containing Regimens Versus CMF in EBCTCG Meta-Analysis

Study (starting year)	Regimens	No. of Cycles	No. of Patients	Doxorubicin-Containing Regimens vs CMF HR (95% CI)	
				DFS	OS
NSABP B-15 (1984)	AC	4	1562*	0.93 (0.82-1.06)	0 97 (0.83-1.12)
	CMF	6	776		
SECSG 2 (1976)	FAC	6	260	0 86 (0.66-1.13)	0.93 (0.69-1.26)
	CMF	6	268		
ONCOFRANCE (1978)	FACV	12	138	0 71 (0.49-1.03)	0.65 (0 44-0 96)
	CMF	12	113		
SE Sweden BCG A (1980)	AC	6	21	0.59 (0.22-1.61)	0.53 (0.21-1.37)
	CMF	6	22		
NSABC Israel Br0283 (1983)	AVb†	4	55	0.91 (0.53-1.57)	0.88 (0 47-1 63)
	CMF	6			
	CMF	6	50		
Austrian BCSG 3 (1984)	CMFVA	6	121	1.07 (0.73-1.55)	0 93 (0 64-1.35)
	CMF	8	124		
Combined Studies	Doxorubicin-Containing Regimens		2157	**0.91 (0.82-1.01)**	**0.91 (0.81-1.03)**
	CMF		1353		

Abbreviations: DFS = disease free survival, OS = overall survival; AC = doxorubicin, cyclophosphamide; AVbCMF = doxorubicin, vinblastine, cyclophosphamide, methotrexate, 5-fluorouracil; CMF = cyclophosphamide, methotrexate, 5-fluorouracil, CMFVA = cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, doxorubicin, FAC = 5-fluorouracil, doxorubicin, cyclophosphamide; FACV = 5-fluorouracil, doxorubicin, cyclophosphamide, vincristine; HR = hazard ratio; CI = confidence interval

* Includes pooled data from patients who received either AC alone for 4 cycles, or who were treated with AC for 4 cycles followed by 3 cycles of CMF.

† Patients received alternating cycles of AVb and CMF.

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191 **Figure 1. Meta-analysis of Disease-Free Survival**

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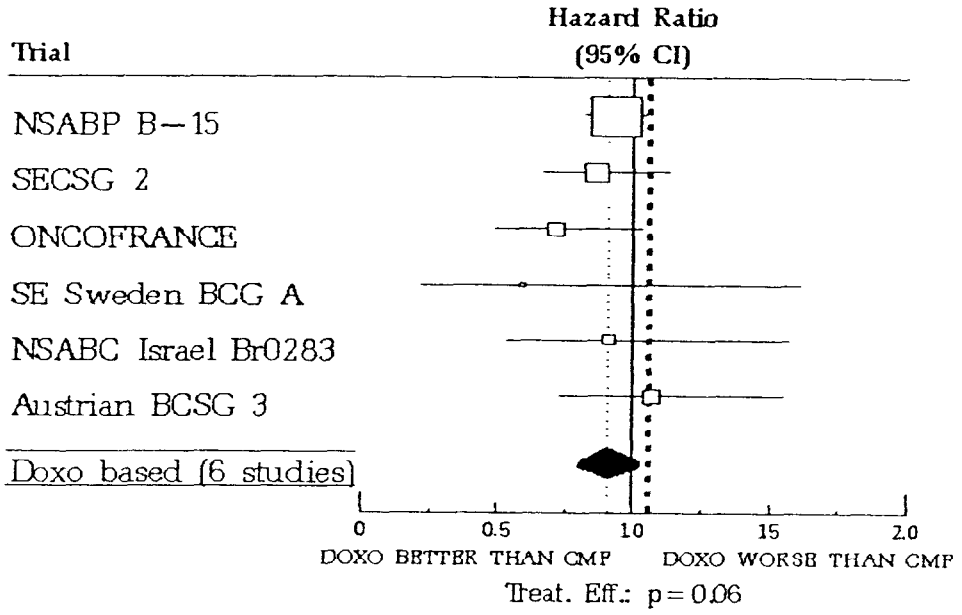

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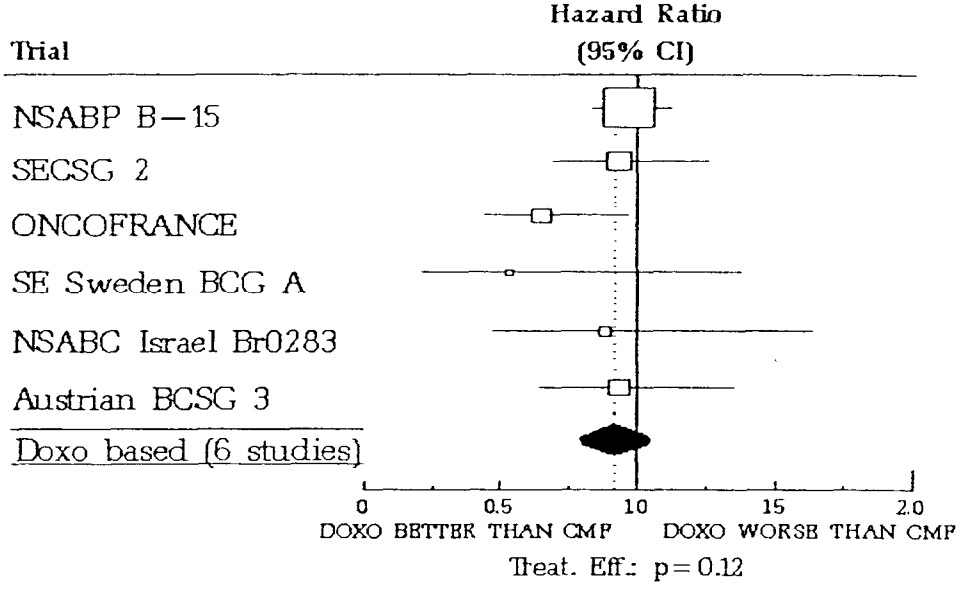
Figure 2. Meta-analysis of Overall Survival



With respect to DFS, 2 of 6 studies (NSABP B-15 and ONCOFRANCE) met the non-inferiority standard individually and with respect to OS, 1 study met the non-inferiority margin individually (ONCOFRANCE). The largest of the 6 studies in the EBCTCG meta-analysis, a randomized, open-label, multicenter trial (NSABP B-15) was conducted in approximately 2300 women (80% premenopausal; 20% postmenopausal) with early breast cancer involving axillary lymph nodes. In this trial, 6 cycles of conventional CMF was compared to 4 cycles of doxorubicin and cyclophosphamide (AC) and 4 cycles of AC followed by 3 cycles of CMF. No statistically significant differences in terms of DFS or OS were observed. (See Table 1).

INDICATIONS AND USAGE

Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease,

malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types.

Doxorubicin is also indicated for use as a component of adjuvant therapy in women with evidence of axillary lymph node involvement following resection of primary breast cancer.

CONTRAINDICATIONS

Patients should not be treated with doxorubicin if they have any of the following conditions: baseline neutrophil count <1500 cells/mm^3; severe hepatic impairment; recent myocardial infarction; severe myocardial insufficiency; severe arrhythmias; previous treatment with complete cumulative doses of doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones; or hypersensitivity to doxorubicin, any of its excipients, or other anthracyclines or anthracenediones. **[See WARNINGS and DOSAGE AND ADMINISTRATION]**

WARNINGS

General

Doxorubicin should be administered only under the supervision of qualified physicians experienced in the use of cytotoxic therapy. Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalized infections) before beginning treatment with doxorubicin. Also, initial treatment with doxorubicin should be preceded by a careful baseline assessment of blood counts; serum levels of total bilirubin, AST, and creatinine; and cardiac function as measured by left ventricular ejection function (LVEF). Patients should be carefully monitored during treatment for possible clinical complications due to myelosuppression. Supportive care may be necessary for the treatment of severe neutropenia and severe infectious complications. Monitoring for potential cardiotoxicity is also important, especially with greater cumulative exposure to doxorubicin. Doxorubicin may potentiate the toxicity of other anticancer therapies (see PRECAUTIONS, Drug Interactions).

Cardiac Function

Cardiotoxicity is a known risk of anthracycline treatment. Anthracycline-induced cardiotoxicity may be manifested by early (or acute) or late (delayed) events.

Early cardiotoxicity of doxorubicin consists mainly of sinus tachycardia and/or electrocardiogram (ECG) abnormalities such as non-specific ST-T wave changes. Tachyarrhythmias, including premature ventricular contractions and ventricular tachycardia, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. These effects do not usually predict subsequent development of delayed cardiotoxicity, are rarely of clinical importance, and are generally not considered an indication for the suspension of doxorubicin treatment.

Delayed cardiotoxicity usually develops late in the course of therapy with doxorubicin or within 2 to 3 months after treatment termination, but later events, several months to years after completion of treatment, have also been reported. Delayed cardiomyopathy is manifested by a reduction in LVEF and/or signs and symptoms of congestive heart failure (CHF) such as tachycardia, dyspnea, pulmonary edema, dependent edema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug.

The probability of developing impaired myocardial function, based on a combined index of signs, symptoms and decline in left ventricular ejection fraction (LVEF) is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m^2 of doxorubicin, 3 to 5% at a dose of 400 mg/m^2, 5 to 8% at a dose of 450 mg/m^2 and 6 to 20% at a dose of 500 mg/m^2 given in a schedule of a bolus injection once every 3 weeks. In a retrospective review, the probability of developing congestive heart failure was reported to be 5/168 (3%) at a cumulative dose of 430 mg/m^2 of doxorubicin, 8/110 (7%) at 575 mg/m^2, and 3/14 (21%) at 728 mg/m^2. In a prospective study of doxorubicin in combination with cyclophosphamide, fluorouracil and/or vincristine in patients with breast cancer or small cell lung cancer, the probability of CHF at various cumulative doses of doxorubicin was 1.5% at 300 mg/m^2, 4.9% at 400 mg/m^2, 7.7%

at 450 mg/m^2 and 20.5% at 500 mg/m^2. The risk of developing CHF increases rapidly with increasing total cumulative doses of doxorubicin in excess of 400 mg/m^2.

Cardiotoxicity may occur at lower doses in patients with prior mediastinal/pericardial irradiation, concomitant use of other cardiotoxic drugs, doxorubicin exposure at an early age, and advanced age. Data also suggest that pre-existing heart disease is a cofactor for increased risk of doxorubicin cardiotoxicity. In such cases, cardiac toxicity may occur at doses lower than the recommended cumulative dose of doxorubicin. Studies have suggested that concomitant administration of doxorubicin and calcium channel entry blockers may increase the risk of doxorubicin cardiotoxicity. The total dose of doxorubicin administered to the individual patient should also take into account previous or concomitant therapy with related compounds such as daunorubicin, idarubicin and mitoxantrone. Although not formally tested, it is probable that the toxicity of doxorubicin and other anthracyclines or anthracenediones is additive. Cardiomyopathy and/or congestive heart failure may be encountered several months or years after discontinuation of doxorubicin therapy.

The risk of acute manifestations of doxorubicin cardiotoxicity in pediatric patients may be as much or lower than in adults. Pediatric patients appear to be at particular risk for developing delayed cardiac toxicity in that doxorubicin- induced cardiomyopathy impairs myocardial growth as pediatric patients mature, subsequently leading to possible development of congestive heart failure during early adulthood. As many as 40% of pediatric patients may have subclinical cardiac dysfunction and 5 to 10% of pediatric patients may develop congestive heart failure on long term follow-up. This late cardiac toxicity may be related to the dose of doxorubicin. The longer the length of follow-up, the greater the increase in the detection rate. Treatment of doxorubicin-induced congestive heart failure includes the use of digitalis, diuretics, after load reducers such as angiotensin I converting enzyme (ACE) inhibitors, low salt diet, and bed rest. Such intervention may relieve symptoms and improve the functional status of the patient.

Monitoring Cardiac Function. The risk of serious cardiac impairment may be decreased through regular monitoring of LVEF during the course of treatment with prompt discontinuation of doxorubicin at the first sign of impaired function. The preferred method

for assessment of cardiac function is evaluation of LVEF measured by multi-gated radionuclide angiography (MUGA) or echocardiography (ECHO). An ECG may also be done. A baseline cardiac evaluation with a MUGA scan or an ECHO is recommended, especially in patients with risk factors for increased cardiac toxicity. Repeated MUGA or ECHO determinations of LVEF should be performed, particularly with higher, cumulative anthracycline doses. The technique used for assessment should be consistent through follow-up. In patients with risk factors, particularly prior anthracycline or anthracenedione use, the monitoring of cardiac function must be particularly strict and the risk-benefit of continuing treatment with doxorubicin in patients with impaired cardiac function must be carefully evaluated.

Endomyocardial biopsy is recognized as the most sensitive diagnostic tool to detect anthracycline-induced cardiomyopathy; however, this invasive examination is not practically performed on a routine basis. ECG changes such as dysrhythmias, a reduction of the QRS voltage, or a prolongation beyond normal limits of the systolic time interval may be indicative of anthracycline-induced cardiomyopathy, but ECG is not a sensitive or specific method for following anthracycline-related cardiotoxicity.

Pediatric patients are at increased risk for developing delayed cardiotoxicity following doxorubicin administration and therefore a follow-up cardiac evaluation is recommended periodically to monitor for this delayed cardiotoxicity.

In adults, a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function. In pediatric patients, deterioration in cardiac function during or after the completion of therapy with doxorubicin is indicated by a drop in fractional shortening (FS) by an absolute value of $\geq$10 percentile units or below 29%, and a decline in LVEF of 10 percentile units or an LVEF below 55%. In general, if test results indicate deterioration in cardiac function associated with doxorubicin, the benefit of continued therapy should be carefully evaluated against the risk of producing irreversible cardiac damage. Acute life-threatening arrhythmias have been reported to occur during or within a few hours after doxorubicin administration.

341 **Hematologic Toxicity**

342 As with other cytotoxic agents, doxorubicin may produce myelosuppression.
343 Myelosuppression requires careful monitoring. Total and differential WBC, red blood cell
344 (RBC), and platelet counts should be assessed before and during each cycle of therapy with
345 doxorubicin. A dose-dependent, reversible leukopenia and/or granulocytopenia
346 (neutropenia) are the predominant manifestations of doxorubicin hematologic toxicity and is
347 the most common acute dose-limiting toxicity of this drug. With the recommended dose
348 schedule, leukopenia is usually transient, reaching its nadir 10 to 14 days after treatment with
349 recovery usually occurring by the 21st day. Thrombocytopenia and anemia may also occur.
350 Clinical consequences of severe myelosuppression include fever, infections,
351 sepsis/septicemia, septic shock, hemorrhage, tissue hypoxia, or death.
352

353 **Secondary Leukemia**

354 The occurrence of secondary AML or MDS has been reported most commonly in patients
355 treated with chemotherapy regimens containing anthracyclines (including doxorubicin) and
356 DNA-damaging antineoplastic agents, in combination with radiotherapy, when patients have
357 been heavily pretreated with cytotoxic drugs, or when doses of anthracyclines have been
358 escalated. Such cases generally have a 1-3 year latency period. The rate of developing
359 secondary AML or MDS has been estimated in an analysis of 8563 patients with early breast
360 cancer treated in 6 studies conducted by the National Surgical Adjuvant Breast and Bowel
361 Project (NSABP), including NSABP B-15. Patients in these studies received standard doses
362 of doxorubicin and standard or escalated doses of cyclophosphamide (AC) adjuvant
363 chemotherapy and were followed for 61,810 patient years. Among 4483 such patients who
364 received conventional doses of AC, 11 cases of AML or MDS were identified, for an
365 incidence of 0.32 cases per 1000 patient years (95% CI 0.16-0.57) and a cumulative
366 incidence at 5 years of 0.21% (95% CI 0.11-0.41%). In another analysis of 1474 patients
367 with breast cancer who received adjuvant treatment with doxorubicin-containing regimens in
368 clinical trials conducted at University of Texas M.D. Anderson Cancer Center, the incidence
369 was estimated at 1.5% at 10 years. In both experiences, patients who received regimens with
370 higher cyclophosphamide dosages, who received radiotherapy, or who were aged 50 or older
371 had an increased risk of secondary AML or MDS.
372

Pediatric patients are also at risk of developing secondary AML.

Effects at Site of Injection

Phlebosclerosis may result from an injection into a small vessel or from repeated injections into the same vein. Following the recommended administration procedures may minimize the risk of phlebitis/thrombophlebitis at the injection site (see DOSAGE AND ADMINISTRATION, Instruction for Use/Handling).

Extravasation

On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein (see DOSAGE AND ADMINISTRATION).

Hepatic Impairment

Since metabolism and excretion of doxorubicin occurs predominantly by the hepatobiliary route, toxicity of recommended doses of doxorubicin can be enhanced by hepatic impairment; therefore, prior to individual dosing, evaluation of hepatic function is recommended using conventional laboratory tests such as SGOT, SGPT, alkaline phosphatase, and bilirubin (see DOSAGE AND ADMINISTRATION).

Pregnancy Category D

Doxorubicin can cause fetal harm when administered to a pregnant woman. Doxorubicin was teratogenic and embryotoxic at doses of 0.8 mg/kg/day (about 1/13 the recommended human dose on a body surface area basis) when administered during the period of organogenesis in rats. Teratogenicity and embryotoxicity were also seen using discrete periods of treatment. The most susceptible was the 6- to 9-day gestation period at doses of 1.25 mg/kg/day and greater. Characteristic malformations included esophageal and intestinal atresia, tracheo-esophageal fistula, hypoplasia of the urinary bladder and cardiovascular anomalies. Doxorubicin was embryotoxic (increase in embryofetal deaths) and abortifacient at 0.4

mg/kg/day (about 1/14 the recommended human dose on a body surface area basis) in rabbits when administered during the period of organogenesis.

There are no adequate and well-controlled studies in pregnant women. If doxorubicin is to be used during pregnancy, or if the patient becomes pregnant during therapy, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Doxorubicin is not an anti-microbial agent. Doxorubicin is emetigenic. Antiemetics may reduce nausea and vomiting; prophylactic use of antiemetics should be considered before administration of doxorubicin, particularly when given in conjunction with other emetigenic drugs.

Information for Patients

Patients should be informed of the expected adverse effects of doxorubicin, including gastrointestinal symptoms (nausea, vomiting, diarrhea, and stomatitis) and potential neutropenic complications. Patients should consult their physician if vomiting, dehydration, fever, evidence of infection, symptoms of CHF, or injection-site pain occurs following therapy with doxorubicin. Patients should be informed that they will almost certainly develop alopecia. Patients should be advised that their urine may appear red for 1 to 2 days after administration of doxorubicin and that they should not be alarmed. Patients should understand that there is a risk of irreversible myocardial damage associated with treatment with doxorubicin, as well as a risk of treatment-related leukemia. Because doxorubicin may induce chromosomal damage in sperm, men undergoing treatment with doxorubicin should use effective contraceptive methods. Women treated with doxorubicin may develop irreversible amenorrhea, or premature menopause.

Drug Interactions

Doxorubicin is extensively metabolized by the liver. Changes in hepatic function induced by concomitant therapies may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy, and/or toxicity. Toxicities associated with doxorubicin, especially hematologic and gastrointestinal events, may be increased when doxorubicin is used in combination with other cytotoxic drugs.

Paclitaxel: There have been a number of reports in the literature that describe an increase in cardiotoxicity when doxorubicin is co-administered with paclitaxel. Two published studies report that initial administration of paclitaxel infused over 24 hours followed by doxorubicin administered over 48 hours resulted in a significant decrease in doxorubicin clearance with more profound neutropenic and stomatitis episodes than the reverse sequence of administration.

Progesterone: In a published study, progesterone was given intravenously to patients with advanced malignancies (ECOG PS<2) at high doses (up to 10 g over 24 hours) concomitantly with a fixed doxorubicin dose (60 mg/m^2) via bolus injection. Enhanced doxorubicin-induced neutropenia and thrombocytopenia were observed.

Verapamil: A study of the effects of verapamil on the acute toxicity of doxorubicin in mice revealed higher initial peak concentrations of doxorubicin in the heart with a higher incidence and severity of degenerative changes in cardiac tissue resulting in a shorter survival.

Cyclosporine: The addition of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than doxorubicin alone. Coma and/or seizures have also been described.

Dexrazoxane: In a clinical study of women with metastatic breast cancer, the concurrent use of the cardioprotectant, dexrazoxane, with the initiation of a regimen of fluorouracil, doxorubicin, and cyclophosphamide (FAC) was associated with a lower tumor response rate. Later initiation of dexrazoxane (after administration of a cumulative doxorubicin dose of 300 mg/m^2 of doxorubicin had been given as a component of FAC) was not associated with a reduction in chemotherapy activity. Dexrazoxane is only indicated for use in women with

metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2 and are continuing with doxorubicin therapy.

Cytarabine: Necrotizing colitis manifested by typhlitis (cecal inflammation), bloody stools and severe and sometimes fatal infections have been associated with a combination of doxorubicin given by intravenous push daily for 3 days and cytarabine given by continuous infusion daily for 7 or more days.

Cyclophosphamide: The addition of cyclophosphamide to doxorubicin treatment does not affect exposure to doxorubicin, but may result in an increase in exposure to doxorubicinol, a metabolite. Doxorubicinol only has 5% of the cytotoxic activity of doxorubicin. Concurrent treatment with doxorubicin has been reported to exacerbate cyclophosphamide-induced hemorrhagic cystitis. Acute myeloid leukemia has been reported as a second malignancy after treatment with doxorubicin and cyclophosphamide.

Literature reports have also described the following drug interactions: Phenobarbital increases the elimination of doxorubicin; phenytoin levels may be decreased by doxorubicin; streptozocin (Zanosar®) may inhibit hepatic metabolism of doxorubicin; saquinavir in combination with cyclophosphamide, doxorubicin, and etoposide increased mucosal toxicity in patients with HIV-associated non-Hodgkin's lymphoma; and administration of live vaccines to immunosuppressed patients including those undergoing cytotoxic chemotherapy may be hazardous.

Laboratory Tests

Initial treatment with doxorubicin requires observation of the patient and periodic monitoring of complete blood counts, hepatic function tests, and left ventricular ejection fraction. (See WARNINGS). Abnormalities of hepatic function tests may occur. Like other cytotoxic drugs, doxorubicin may induce "tumor lysis syndrome" and hyperuricemia in patients with rapidly growing tumors. . Blood uric acid levels, potassium, calcium, phosphate, and creatinine should be evaluated after initial treatment. Hydration, urine alkalinization, and prophylaxis with allopurinol to prevent hyperuricemia may minimize potential complications of tumor-lysis syndrome.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity studies have not been conducted with doxorubicin. Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) have been reported in patients treated with doxorubicin-containing combination chemotherapy regimens (see WARNINGS). Pediatric patients treated with doxorubicin or other topoisomerase II inhibitors are at risk for developing acute myelogenous leukemia and other neoplasms. Doxorubicin was mutagenic in the in vitro Ames assay, and clastogenic in multiple in vitro assays (CHO cell, V79 hamster cell, human lymphoblast, and SCE assays) and the in vivo mouse micronucleus assay.

Doxorubicin decreased fertility in female rats at the doses of 0.05 and 0.2 mg/kg/day (about 1/200 and 1/50 the recommended human dose on a body surface area basis) when administered from 14 days before mating through late gestation period. A single i.v. dose of doxorubicin at 0.1 mg/kg (about 1/100 the recommended human dose on a body surface area basis) was toxic to male reproductive organs producing testicular atrophy and oligospermia in rats. Doxorubicin is mutagenic as it induced DNA damage in rabbit spermatozoa and dominant lethal mutations in mice. Therefore, doxorubicin may potentially induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia were evidenced in men treated with doxorubicin, mainly in combination therapies. Men undergoing doxorubicin treatment should use effective contraceptive methods.

Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia. Doxorubicin is mutagenic as it induces DNA damage in rabbit spermatozoa and dominant lethal mutations in mice. Therefore, doxorubicin can potentially induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia were evidenced in men treated with doxorubicin, mainly in combination therapies. This effect may be permanent. However, sperm counts have been reported to return to normal levels in some instances. This may occur several years after the end of the therapy. Men undergoing doxorubicin treatment should use effective contraceptive methods.

In women, doxorubicin may cause infertility during the time of drug administration. Doxorubicin may cause amenorrhea. Ovulation and menstruation may return after termination of therapy, although premature menopause can occur. Recovery of menses is related to age at treatment.

Secondary acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) have been reported in patients treated with anthracycline-containing adjuvant combination chemotherapy regimens (see WARNINGS, Hematologic).

Pregnancy Category D

(See WARNINGS.)

Nursing Mothers

Doxorubicin and its major metabolite, doxorubicinol have been detected in the milk of at least one lactating patient (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Because of the potential for serious adverse reactions in nursing infants from doxorubicin, mothers should be advised to discontinue nursing during doxorubicin therapy.

Pediatric Use

Pediatric patients are at increased risk for developing delayed cardiotoxicity. Follow-up cardiac evaluations are recommended periodically to monitor for this delayed cardiotoxicity (see WARNINGS). Doxorubicin, as a component of intensive chemotherapy regimens administered to pediatric patients, may contribute to prepubertal growth failure. It may also contribute to gonadal impairment, which is usually temporary. Pediatric patients treated with doxorubicin or other topoisomerase II inhibitors are at a risk for developing acute myelogenous leukemia and other neoplasms. Pediatric patients receiving concomitant doxorubicin and actinomycin-D have manifested acute "recall" pneumonitis at variable times after local radiation therapy.

Geriatric Use

An estimated 4600 patients who were 65 and over were included in the reported clinical experience of doxorubicin use for various indications. No overall differences in safety and

559 effectiveness were observed between these patients and younger patients, but greater
560 sensitivity of some older individuals cannot be ruled out. The decision to use doxorubicin in
561 the treatment of older patients should be based upon a consideration of overall performance
562 status and concurrent illnesses, in addition to age of the individual patient.
563
564
565 ## ADVERSE REACTIONS
566 Dose limiting toxicities of therapy are myelosuppression and cardiotoxicity. Other reactions
567 reported are:
568 *Cardiotoxicity* - (See WARNINGS.)
569 *Cutaneous* - Reversible complete alopecia occurs in most cases. Hyperpigmentation of
570 nailbeds and dermal creases, primarily in pediatric patients, and onycholysis have been
571 reported in a few cases. Radiation recall reaction has occurred with doxorubicin
572 administration. Rash, itching, or photosensitivity may occur.
573 *Gastrointestinal* - Acute nausea and vomiting occurs frequently and may be severe. This
574 may be alleviated by antiemetic therapy. Mucositis (stomatitis and esophagitis) may occur
575 within 5 to 10 of beginning therapy, and most patients recover from this adverse event within
576 another 5 to 10 days. The effect may be severe leading to ulceration and represents a site of
577 origin for severe infections. The dosage regimen consisting of administration of doxorubicin
578 on three successive days results in greater incidence and severity of mucositis. Ulceration
579 and necrosis of the colon, especially the cecum, may occur leading to bleeding or severe
580 infections which can be fatal. This reaction has been reported in patients with acute non-
581 lymphocytic leukemia treated with a 3-day course of doxorubicin combined with cytarabine.
582 Anorexia, abdominal pain, dehydration, diarrhea, and hyperpigmentation of the oral mucosa
583 have been occasionally reported.
584 *Hematologic* - (See WARNINGS)
585 *Hypersensitivity* - Fever, chills and urticaria have been reported occasionally. Anaphylaxis
586 may occur. A case of apparent cross sensitivity to lincomycin has been reported.
587 *Neurological* - Peripheral neurotoxicity in the form of local-regional sensory and/or motor
588 disturbances have been reported in patients treated intra-arterially with doxorubicin, mostly
589 in combination with cisplatin. Animal studies have demonstrated seizures and coma in
590 rodents and dogs treated with intra-carotid doxorubicin. Seizures and coma have been
591 reported in patients treated with doxorubicin in combination with cisplatin or vincristine.

Ocular - Conjunctivitis, keratitis, and lacrimation occur rarely.

Other - Malaise/asthenia have been reported.

Adverse Reactions in Patients with Early Breast Cancer Receiving Doxorubicin-Containing Adjuvant Therapy: Safety data were collected from approximately 2300 women who participated in a randomized, open-label trial (NSABP B-15) evaluating the use of AC versus CMF in the treatment of early breast cancer involving axillary lymph nodes. In the safety analysis, the follow-up data from all patients receiving AC were combined (N=1492 evaluable patients) and compared with data from patients receiving conventional CMF (i.e., oral cyclophosphamide; N=739 evaluable patients). The most relevant adverse events reported in this study are provided in Table 2.

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Table 2. Relevant Adverse Events in Patients with Early Breast Cancer Involving Axillary Lymph Nodes

	AC*	Conventional CMF
	N=1492	N=739
Treatment administration		
Mean number of cycles	3 8	5.5
Total cycles	5676	4068
Adverse events, % of patients		
Leukopenia		
Grade 3 (1,000-1,999 /mm^3)	3.4	9.4
Grade 4 (<1000 /mm^3)	0.3	0.3
Thrombocytopenia		
Grade 3 (25,000-49,999 /mm^3)	0	0.3
Grade 4 (<25,000 /mm^3)	0.1	0
Shock, sepsis	1.5	0.9
Systemic infection	2.4	1.2
Nausea and vomiting		
Nausea only	15.5	42.8
Vomiting ≤12 hours	34.4	25.2
Vomiting >12 hours	36 8	12.0
Intractable	4.7	1.6
Alopecia	92 4	71.4
Partial	22.9	56.3
Complete	69.5	15.1
Weight loss		
5-10%	6.2	5 7
>10%	2.4	2.8
Weight gain		
5-10%	10.6	27.9
>10%	3.8	14.3
Cardiac function		
Asymptomatic	0.2	0 1
Transient	0.1	0
Symptomatic	0.1	0
Treatment-related death	0	0

* Includes pooled data from patients who received either AC alone for 4 cycles, or who were treated with AC for 4 cycles followed by 3 cycles of CMF

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605

606 ## OVERDOSAGE

607 Acute overdosage with doxorubicin enhances the toxic effect of mucositis, leukopenia and
608 thrombocytopenia. Treatment of acute overdosage consists of treatment of the severely
609 myelosuppressed patient with hospitalization, antimicrobials, platelet transfusions and
610 symptomatic treatment of mucositis. Use of hemopoietic growth factor (G-CSF, GM-CSF)
611 may be considered. The 150 mg doxorubicin hydrochloride for injection and the 75 mL and
612 100 mL (2 mg/mL) doxorubicin hydrochloride injection vials are packaged as multiple dose

vials and caution should be exercised to prevent inadvertent overdosage. Cumulative dosage with doxorubicin increases the risk of cardiomyopathy and resultant congestive heart failure (see WARNINGS). Treatment consists of vigorous management of congestive heart failure with digitalis preparations, diuretics, and after-load reducers such as ACE inhibitors.

DOSAGE AND ADMINISTRATION

Care in the administration of doxorubicin will reduce the chance of perivenous infiltration (see WARNINGS). It may also decrease the chance of local reactions such as urticaria and erythematous streaking. On intravenous administration of doxorubicin, extravasation may occur with or without an accompanying burning or stinging sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the injection or infusion should be immediately terminated and restarted in another vein. If extravasation is suspected, intermittent application of ice to the site for 15 min. q.i.d. x 3 days may be useful. The benefit of local administration of drugs has not been clearly established. Because of the progressive nature of extravasation reactions, close observation and plastic surgery consultation is recommended. Blistering, ulceration and/or persistent pain are indications for wide excision surgery, followed by split-thickness skin grafting.

The most commonly used dose schedule when used as a single agent is 60 to 75 mg/m^2 as a single intravenous injection administered at 21-day intervals. The lower dosage should be given to patients with inadequate marrow reserves due to old age, or prior therapy, or neoplastic marrow infiltration.

Doxorubicin has been used concurrently with other approved chemotherapeutic agents. Evidence is available that in some types of neoplastic disease combination chemotherapy is superior to single agents. The benefits and risks of such therapy continue to be elucidated. When used in combination with other chemotherapy drugs, the most commonly used dosage of doxorubicin is 40 to 60 mg/m^2 given as a single intravenous injection every 21 to 28 days.

In a large randomized study (NSABP B-15) of patients with early breast cancer involving axillary lymph nodes (see CLINICAL PHARMACOLOGY, Clinical Studies and ADVERSE

REACTIONS, Adverse Reactions in Patients with Early Breast Cancer Receiving Doxorubicin-Containing Adjuvant Therapy), the combination dosage regimen of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) was administered intravenously on day 1 of each 21-day treatment cycle. Four cycles of treatment were administered

Dose Modifications

Patients in the NSABP B-15 study could have dose modifications of AC to 75% of the starting doses for neutropenic fever/infection. When necessary, the next cycle of treatment cycle was delayed until the absolute neutrophil count (ANC) was ≥1000 cells/mm^3 and the platelet count was ≥100□000 cells/mm^3 and nonhematologic toxicities had resolved.

Doxorubicin dosage must be reduced in case of hyperbilirubinemia as follows:

Plasma bilirubin concentration (mg/dL)	Dosage reduction (%)
1.2 - 3.0	50
3.1 - 5.0	75

Reconstitution Directions

It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. The rate of administration is dependent on the size of the vein, and the dosage. However, the dose should be administered in not less than 3 to 5 minutes. Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid an administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein. Perivenous infiltration may occur painlessly.

Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin. Until specific

compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Handling and Disposal

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published.[1-8] There is no general agreement that all the procedures recommended in the guidelines are necessary or appropriate. However, given the toxic nature of this substance, the following protective recommendations are provided:

- Personnel should be trained in good technique for reconstitution and handling.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling doxorubicin should wear protective clothing: goggles, gowns and disposable gloves and masks.
- A designated area should be defined for reconstitution (preferably under a laminar flow system). The work surface should be protected by disposable, plastic-backed, absorbent paper.
- All items used for reconstitution, administration or cleaning, including gloves, should be placed in high-risk waste-disposal bags for high-temperature incineration.
- Spillage or leakage should be treated with dilute sodium hypochlorite (1% available chlorine) solution, preferably by soaking, and then water.
- All cleaning materials should be disposed of as indicated previously.
- In case of skin contact thoroughly wash the affected area with soap and water or sodium bicarbonate solution. However, do not abrade the skin by using a scrub brush
- In case of contact with the eye(s), hold back the eyelid(s) and flush the affected eye(s) with copious amounts of water for at least 15 minutes. Then seek medical evaluation by a physician.
- Always wash hands after removing gloves.

Caregivers of pediatric patients receiving doxorubicin should be counseled to take precautions (such as wearing latex gloves) to prevent contact with the patient's urine and other body fluids for at least 5 days after each treatment.

HOW SUPPLIED

Doxorubicin Hydrochloride for Injection, USP, a sterile red-orange lyophilized powder for intravenous use only, is available in 10, 20 and 50 mg single dose vials and a 150 mg multidose vial.

Each 10 mg single dose vial contains 10 mg of doxorubicin HCl, USP, 50 mg of lactose, NF (hydrous) and 1 mg of methylparaben, NF (added to enhance dissolution).

Each 20 mg single dose vial contains 20 mg of doxorubicin HCl, USP, 100 mg of lactose, NF (hydrous) and 2 mg of methylparaben, NF (added to enhance dissolution).

Each 50 mg single dose vial contains 50 mg of doxorubicin HCl, USP, 250 mg of lactose, NF (hydrous) and 5 mg of methylparaben, NF (added to enhance dissolution).

Each 150 mg multidose vial contains 150 mg of doxorubicin HCl, USP, 750 mg of lactose, NF (hydrous) and 15 mg of methylparaben, NF (added to enhance dissolution).

Doxorubicin Hydrochloride for Injection, USP is available as:

Sterile single use only:

NDC 0013-1086-91 10 mg single dose vial, 10 vial packs

NDC 0013-1096-91 20 mg single dose vial, 10 vial packs

NDC 0013-1106-79 50 mg single dose vial, single packs

Multidose vial:

NDC 0013-1116-83 150 mg multidose vial, single packs

Store at controlled room temperature, 15° to 30°C (59° to 86°F). Protect from light. Retain in carton until time of use. Discard unused portion.

Reconstituted Solution Stability

After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and under normal room light

(100 foot-candles) and 15 days under refrigeration (2° to 8°C). It should be protected from exposure to sunlight. Discard any unused solution from the 10 mg, 20 mg and 50 mg single dose vials. Unused solutions of the multiple dose vial remaining beyond the recommended storage times should be discarded.

Doxorubicin Hydrochloride Injection, USP, is a sterile parenteral, isotonic, available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg), and 37.5 mL (75 mg) single dose vials and a 100 mL (200 mg) multidose vial. Each mL contains doxorubicin HCl and the following inactive ingredients: sodium chloride 0.9% and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target pH of 3.0.

Doxorubicin Hydrochloride Injection, USP is available as:

SINGLE DOSE GLASS VIALS:

NDC 0013-1136-91 10 mg vial, 2 mg/mL, 5 mL, 10 vial packs

NDC 0013-1146-91 20 mg vial, 2 mg/mL,10 mL, 10 vial packs

NDC 0013-1156-79 50 mg vial, 2 mg/mL, 25 mL, single vial packs

NDC 0013-1176-87 75 mg vial, 2 mg/mL, 37.5 mL, single vial packs

MULTIDOSE VIALS, in Cytosafe™ vial packs:

NDC 0013-1286-83 150 mg, 2 mg/mL, 75 mL

NDC 0013-1266-83 200 mg, 2 mg/mL, 100 mL

Store refrigerated, 2° to 8°C (36° to 46°F). Protect from light. Retain in carton until contents are used. Contains no preservative. Discard unused portion.

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.

2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. JAMA 1985; 2.53(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure-Recommendations for Handling of Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

4. Clinical Oncology Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia 1983; 1:426-428.

5. Jones RB, et al. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA-A Cancer Journal for Clinicians 1983; (Sept/Oct): 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm 1990; 47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines). Am J Health-Syst Pharm 1996; 53:1669-1685.

8. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, PA: Oncology Nursing Society; 1999: 32-41.

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BEDFORD LABORATORIES™

DAUNORUBICIN HYDROCHLORIDE INJECTION

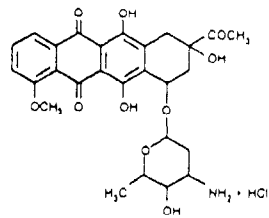
Rx ONLY.

WARNINGS

1. Daunorubicin Hydrochloride Injection must be given into a rapidly flowing intravenous infusion. It must *never* be given by the intramuscular or subcutaneous route. Severe local tissue necrosis will occur if there is extravasation during administration.
2. Myocardial toxicity manifested in its most severe form by potentially fatal congestive heart failure may occur either during therapy or months to years after termination of therapy. The incidence of myocardial toxicity increases after a total cumulative dose exceeding 400 to 550 mg/m² in adults, 300 mg/m² in children more than 2 years of age, or 10 mg/kg in children less than 2 years of age.
3. Severe myelosuppression occurs when used in therapeutic doses; this may lead to infection or hemorrhage.
4. It is recommended that daunorubicin hydrochloride be administered only by physicians who are experienced in leukemia chemotherapy and in facilities with laboratory and supportive resources adequate to monitor drug tolerance and protect and maintain a patient compromised by drug toxicity. The physician and institution must be capable of responding rapidly and completely to severe hemorrhagic conditions and/or overwhelming infection.
5. Dosage should be reduced in patients with impaired hepatic or renal function.

DESCRIPTION

Daunorubicin hydrochloride is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. It is provided as a deep red sterile liquid in vials for intravenous administration only. Each mL contains 5 mg daunorubicin (equivalent to 5.34 mg of daunorubicin hydrochloride), 9 mg sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH), and water for injection, q.s. It has the following structural formula which may be described with the chemical name of (1*S*,3*S*)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl 3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranoside hydrochloride. Its molecular formula is $C_{27}H_{29}NO_{10}$•HCl with a molecular weight of 563.99. It is a hygroscopic crystalline powder. The pH of a 5 mg/mL aqueous solution is 4 to 5.



CLINICAL PHARMACOLOGY

Mechanism of Action: Daunorubicin has antimitotic and cytotoxic activity through a number of proposed mechanisms of action. Daunorubicin forms complexes with DNA by intercalation between base pairs. It inhibits topoisomerase II activity by stabilizing the DNA-topoisomerase II complex, preventing the religation portion of the ligation-religation reaction that topoisomerase II catalyzes. Single strand and double strand DNA breaks result.

Daunorubicin hydrochloride may also inhibit polymerase activity, affect regulation of gene expression, and produce free radical damage to DNA.

Daunorubicin hydrochloride possesses an antitumor effect against a wide spectrum of animal tumors, either grafted or spontaneous.

Pharmacokinetics

General. Following intravenous injection of Daunorubicin hydrochloride, plasma levels of daunorubicin decline rapidly, indicating rapid tissue uptake and concentration. Thereafter, plasma levels decline slowly with a half-life of 45 minutes in the initial phase and 18.5 hours in the terminal phase. By 1 hour after drug administration, the predominant plasma species is daunorubicinol, and active metabolite, which disappears with a half-life of 26.7 hours.

Distribution. Daunorubicin hydrochloride is rapidly and widely distributed in tissues, with highest levels in the spleen, kidneys, liver, lungs, and heart. The drug binds to many cellular components, particularly nucleic acids. There is no evidence that daunorubicin crosses the blood-brain barrier, but the drug apparently crosses the placenta.

Metabolism and Elimination. Daunorubicin hydrochloride is extensively metabolized in the liver and other tissues, mainly by cytoplasmic aldo-keto reductases, producing daunorubicinol, the major metabolite which has antineoplastic activity. Approximately 40% of the drug in the plasma is present as daunorubicinol within 30 minutes and 60% in 4 hours after a dose of daunorubicin. Further metabolism via reduction cleavage of the glycosidic bond, 4-O demethylation, and conjugation with both sulfate and glucuronide have been demonstrated. Simple glycosidic cleavage of daunorubicin or daunorubicinol is not a significant metabolic pathway in man. Twenty-five percent of an administered dose of daunorubicin hydrochloride is eliminated in an active form by urinary excretion and an estimated 40% by biliary excretion.

Special Populations

Pediatric Patients: Although appropriate studies with daunorubicin hydrochloride have not been performed in the pediatric population, cardiotoxicity may be more frequent and occur at lower cumulative doses in children.

Geriatric Patients: Although appropriate studies with daunorubicin hydrochloride have not been performed in the geriatric population, cardiotoxicity may be more frequent in the elderly. Caution should also be used in patients who have inadequate bone marrow reserves due to old age. In addition, elderly patients are more likely to have age-related renal function impairment, which may require reduction of dosage in patients receiving daunorubicin hydrochloride.

Renal and Hepatic Impairment: Doses of daunorubicin hydrochloride should be reduced in patients with hepatic and renal impairment. Patients with serum bilirubin concentrations of 1.2 to 3 mg/dL should receive 75% of the usual daily dose and patients with serum bilirubin concentrations greater than 3 mg/dL should receive 50% of the usual daily dose. Patients with serum creatinine concentrations of greater than 3 mg/dL should receive 50% of the usual daily dose. (See WARNINGS, Evaluation of Hepatic and Renal Function)

Clinical Studies. In the treatment of adult acute nonlymphocytic leukemia, daunorubicin hydrochloride, used as a single agent, has produced complete remission rates of 40 to 50%, and in combination with cytarabine, has produced complete remission rates of 53 to 65%.

The addition of daunorubicin hydrochloride to the two-drug induction regimen of vincristine-prednisone in the treatment of childhood acute lymphocytic leukemia does not increase the rate of complete remission. In children receiving identical CNS prophylaxis and maintenance therapy (without consolidation), there is prolongation of complete remission duration (statistically significant, $p<0.02$) in those children induced with the three drug (daunorubicin-vincristine-prednisone) regimen as compared to two drugs. There is no evidence of any impact of daunorubicin hydrochloride on the duration of complete remission when a consolidation (intensification) phase is employed as part of a total treatment program.

In adult acute lymphocytic leukemia, in contrast to childhood acute lymphocytic leukemia, daunorubicin hydrochloride during induction significantly increases the rate of complete remission, but not remission duration, compared to that obtained with vincristine, prednisone, and L-asparaginase alone. The use of daunorubicin hydrochloride in combination with vincristine, prednisone, and L-asparaginase has produced complete remission rates of 83% in contrast to a 47% remission in patients not receiving daunorubicin hydrochloride.

INDICATIONS AND USAGE

Daunorubicin hydrochloride in combination with other approved antucancer drugs is indicated for remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults.

CONTRAINDICATIONS

Daunorubicin hydrochloride is contraindicated in patients who have shown a hypersensitivity to it.

WARNINGS

Bone Marrow: Daunorubicin hydrochloride is a potent bone marrow suppressant. Suppression will occur in all patients given a therapeutic dose of this drug. Therapy with daunorubicin hydrochloride should not be started in patients with pre-existing drug-induced bone marrow suppression unless the benefit from such treatment warrants the risk. Persistent, severe myelosuppression may result in superinfection or hemorrhage.

Cardiac Effects: Special attention must be given to the potential cardiac toxicity of daunorubicin hydrochloride, particularly in infants and children. Pre-existing heart disease and previous therapy with doxorubicin are co-factors of increased risk of daunorubicin-induced cardiac toxicity and the benefit-to-risk ratio of daunorubicin hydrochloride therapy in such patients should be weighed before starting daunorubicin hydrochloride. In adults, at total cumulative doses less than 550 mg/m², acute congestive heart failure is seldom encountered. However, rare instances of pericarditis-myocarditis, not dose-related, have been reported.

In adults, at cumulative doses exceeding 550 mg/m², there is an increased incidence of drug-induced congestive heart failure. Based on prior clinical experience with doxorubicin, this limit appears lower, namely 400 mg/m² in patients who received radiation therapy that encompassed the heart.

In infants and children, there appears to be a greater susceptibility to anthracycline-induced cardiotoxicity compared to that in adults, which is more clearly dose-related. Anthracycline therapy (including daunorubicin) in pediatric patients has been reported to produce impaired left ventricular systolic performance, reduced contractility, congestive heart failure or death. These conditions may occur months to years following cessation of chemotherapy. This appears to be dose-dependent and aggravated by thoracic irradiation. Long-term periodic evaluation of cardiac function in such patients should, thus, be performed. In both children and adults, the total dose of daunorubicin hydrochloride administered should also take into account any previous or concomitant therapy with other potentially cardiotoxic agents or related compounds such as doxorubicin.

There is no absolutely reliable method of predicting the patients in whom acute congestive heart failure will develop as a result of the cardiac toxic effect of daunorubicin hydrochloride. However, certain changes in the electrocardiogram and a decrease in the systolic ejection fraction from pre-treatment baseline may help to recognize those patients at greatest risk to develop congestive heart failure. On the basis of the electrocardiogram, a decrease equal to or greater than 30% in limb lead QRS voltage has been associated with a significant risk of drug-induced cardiomyopathy. Therefore, an electrocardiogram and/or determination of systolic ejection fraction should be performed before each course of daunorubicin hydrochloride. In the event that one or the other of these predictive parameters should occur, the benefit of continued therapy must be weighed against the risk of producing cardiac damage.

Early clinical diagnosis of drug-induced congestive heart failure appears to be essential for successful treatment.

Evaluation of Hepatic and Renal Function: Significant hepatic or renal impairment can enhance the toxicity of the recommended doses of daunorubicin hydrochloride; therefore, prior to administration, evaluation of hepatic function and renal function using conventional clinical laboratory tests is recommended (see DOSAGE AND ADMINISTRATION section).

Pregnancy: Daunorubicin hydrochloride may cause fetal harm when administered to a pregnant woman. An increased incidence of fetal abnormalities (parieto-occipital cranioschisis, umbilical hernias, or rachischisis) and abortions was reported in rabbits at doses of 0.05 mg/kg/day or approximately 1/100th of the highest recommended human dose on a body surface area basis. Rats showed an increased incidence of esophageal, cardiovascular and urogenital abnormalities as well as rib fusions at doses of 4 mg/kg/day or approximately ½ the human dose on a body surface area basis. Decreases in fetal birth weight and post-delivery growth rate were observed in mice. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Secondary Leukemias: There have been reports of secondary leukemias in patients exposed to topoisomerase II inhibitors when used in combination with other antineoplastic agents or radiation therapy.

Extravasation at Injection Site: Extravasation of daunorubicin hydrochloride at the site of intravenous administration can cause severe local tissue necrosis. (See ADVERSE REACTIONS section.)

PRECAUTIONS

General: Therapy with daunorubicin hydrochloride requires close patient observation and frequent complete blood-count determinations. Cardiac, renal, and hepatic function should be evaluated prior to each course of treatment.

Appropriate measures must be taken to control any systemic infection before beginning therapy with daunorubicin hydrochloride.

Daunorubicin hydrochloride may transiently impart a red coloration to the urine after administration, and patients should be advised to expect this.

Laboratory Tests: Daunorubicin hydrochloride may induce hyperuricemia secondary to rapid lysis of leukemic cells. As a precaution, allopurinol administration is usually begun prior to initiating antileukemic therapy. Blood uric acid levels should be monitored and appropriate therapy initiated in the event that hyperuricemia develops.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Daunorubicin hydrochloride, when injected subcutaneously into mice, causes fibrosarcomas to develop at the injection site. When administered to mice thrice weekly intraperitoneally, no carcinogenic effect was noted after 18 months of observation. In male rats administered daunorubicin thrice weekly for 6 months, at 1/70th the recommended human dose on a body surface area basis, peritoneal sarcomas were found at 18 months. A single IV dose of daunorubicin administered to rats at 1.6 fold the recommended human dose on a body surface area basis caused mammary adenocarcinomas to appear at 1 year. Daunorubicin was mutagenic *in vitro* (Ames assay, V79 hamster cell assay), and clastogenic *in vitro* (CCRFCEM human lymphoblasts) and *in vivo* (SCE assay in mouse bone marrow) tests.

In male dogs at a daily dose of 0.25 mg/kg administered intravenously, testicular atrophy was noted at autopsy. Histologic examination revealed total aplasia of the spermatocyte series in the seminiferous tubules with complete aspermatogenesis.

Pregnancy Category D (See WARNINGS section.)

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from daunorubicin, mothers should be advised to discontinue nursing during daunorubicin therapy.

Elderly: See CLINICAL PHARMACOLOGY, Special Populations, Geriatric Patients section.

Pediatric Use: See CLINICAL PHARMACOLOGY, Special Populations, Pediatric Patients section and WARNINGS, Cardiac Effects section.

Drug Interactions: Use of daunorubicin in a patient who has previously received doxorubicin increases the risk of cardiotoxicity. Daunorubicin hydrochloride should not be used in patients who have previously received the recommended maximum cumulative doses of doxorubicin or daunorubicin hydrochloride. Cyclophosphamide used concurrently with daunorubicin hydrochloride may also result in increased cardiotoxicity.

Dosage reduction of daunorubicin hydrochloride may be required when used concurrently with other myelosuppressive agents.

Hepatotoxic medications, such as high-dose methotrexate, may impair liver function and increase the risk of toxicity.

ADVERSE REACTIONS

Dose-limiting toxicity includes myelosuppression and cardiotoxicity (see **WARNINGS** section). Other reactions include:

Cutaneous: Reversible alopecia occurs in most patients. Rash, contact dermatitis and urticaria have occurred rarely.

Gastrointestinal: Acute nausea and vomiting occur but are usually mild. Antiemetic therapy may be of some help. Mucositis may occur 3 to 7 days after administration. Diarrhea and abdominal pain have occasionally been reported.

Local: If extravasation occurs during administration, severe local tissue necrosis, severe cellulitis, thrombophlebitis, or painful induration can result.

Acute Reactions: Rarely, anaphylactoid reaction, fever, and chills can occur. Hyperuricemia may occur, especially in patients with leukemia, and serum uric acid levels should be monitored.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit.

Principles: In order to eradicate the leukemic cells and induce a complete remission, a profound suppression of the bone marrow is usually required. Evaluation of both the peripheral blood and bone marrow is mandatory in the formulation of appropriate treatment plans.

It is recommended that the dosage of daunorubicin hydrochloride be reduced in instances of hepatic or renal impairment. For example, using serum bilirubin and serum creatinine as indicators of liver and kidney function, the following dose modifications are recommended:

Serum Bilirubin	Serum Creatinine	Dose Reduction
1.2 to 3.0 mg%	—	25%
>3 mg%	—	50%
—	>3 mg%	50%

Representative Dose Schedules and Combination for the Approved Indication of Remission Induction in Adult Acute Nonlymphocytic Leukemia:

In Combination: For patients under age 60, daunorubicin hydrochloride 45 mg/m²/day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m²/day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses.

For patients 60 years of age and above, daunorubicin hydrochloride 30 mg/m²/day IV on days 1, 2, and 3 of the first course and on days 1, 2 of subsequent courses AND cytosine arabinoside 100 mg/m²/day IV infusion daily for 7 days for the first course and for 5 days for subsequent courses. This daunorubicin hydrochloride dose-reduction is based on a single study and may not be appropriate if optimal supportive care is available.

The attainment of a normal-appearing bone marrow may require up to three courses of induction therapy. Evaluation of the bone marrow following recovery from the previous course of induction therapy determines whether a further course of induction treatment is required.

Representative Dose Schedule and Combination for the Approved Indication of Remission Induction in Pediatric Acute Lymphocytic Leukemia:

In Combination: Daunorubicin hydrochloride 25 mg/m² IV on day 1 every week, vincristine 1.5 mg/m² IV on day 1 every week, prednisone 40 mg/m² PO daily. Generally, a complete remission will be obtained within four such courses of therapy, however, if after four courses the patient is in partial remission, an additional one or, if necessary, two courses may be given in an effort to obtain a complete remission.

In children less than 2 years of age or below 0.5 m² body surface area, it has been recommended that the daunorubicin hydrochloride dosage calculation should be based on weight (1 mg/kg) instead of body surface area.

Representative Dose Schedules and Combination for the Approved Indication of Remission Induction in Adult Acute Lymphocytic Leukemia:

In Combination: Daunorubicin hydrochloride 45 mg/m²/day IV on days 1, 2, and 3 AND vincristine 2 mg IV on days 1, 8, and 15, prednisone 40 mg/m²/day PO on days 1 through 22, then tapered between days 22 to 29, L-asparaginase 500 IU/kg/day x 10 days IV on days 22 through 32.

The sterile vial contents provide 20 mg of daunorubicin, with 5 mg of daunorubicin per mL. The desired dose is withdrawn into a syringe containing 10 mL to 15 mL of 0.9% Sodium Chloride Injection, USP and then injected into the tubing or sidearm in a rapidly flowing IV infusion of 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. Daunorubicin hydrochloride should not be administered mixed with other drugs or heparin.

Storage and Handling: Store unopened vials in refrigerator, 2° to 8°C (36° to 46°F). Store prepared solution for infusion at room temperature, 15° to 30°C (59° to 86°F) for up to 24 hours. Contains no preservative. Discard unused portion. **Protect from light.**

If daunorubicin hydrochloride contacts the skin or mucosae, the area should be washed thoroughly with soap and water. Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-7] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

Daunorubicin Hydrochloride Injection, 5 mg/mL, is available as a deep red sterile liquid in butyl-rubber-stoppered vials as follows:

NDC 55390-108-10 20 mg, 4 mL per vial, single-use vials; carton of 10

NDC 55390-108-01 50 mg, 10 mL per vial, single-use vial; individually-boxed

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*, March 15,1985.
3. National Study Commission on Cytotoxic Exposure—Recommendations for Handling Cytotoxic Agents. Available from Louis R. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia* 1:426-428, 1983.
5. Jones RB, et al. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center, Ca—*A Cancer Journal for Clinicians* Sept/Oct, 258-263, 1983.
6. American Society of Hospital Pharmacists technical assistance bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 47:1033-1049, 1990.
7. OSHA Work Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm* 43:1193-1204, 1986.

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